Chronic comorbidities in children and adolescents with perinatally-acquired HIV infection in sub-Saharan Africa in the era of antiretroviral therapy

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Summary

Globally, 1.7 million children are living with HIV, 90% in sub-Saharan Africa (SSA). The remarkable scale-up of combination antiretroviral therapy (ART) has resulted in escalating numbers of children with HIV (CWHIV) reaching adolescence. Unfortunately, in SSA, HIV diagnosis is often delayed with children starting ART late in childhood. In recent years, there have been increasing reports from low-income settings of CWHIV experiencing multisystem chronic comorbidities despite ART. Many of these chronic conditions show clinical phenotypes distinct from those in adults with HIV, and result in disability and reduced quality of life. In this review, we discuss the spectrum and pathogenesis of comorbidities among CWHIV in SSA. Prompt diagnosis and treatment of perinatally acquired HIV infection remains a priority. In addition, there is need for increased awareness of the burden of chronic comorbidities. Diagnostic and therapeutic strategies need to be developed if CWHIV are to achieve their full potential.

Introduction

The HIV pandemic has been established for 40 years and worldwide 1.7 million children were living with HIV in 2018, 90% in sub-Saharan Africa (SSA). The vast majority have been infected by mother-to-child transmission.[1] Due to the remarkable scale-up of effective prevention of mother-to-child transmission interventions, the number of perinatally-acquired HIV (PHIV) infections dropped from 280,000 in 2010 to 160,000 in 2018.[1] At the same time over the past decade, access to combination antiretroviral therapy (ART) (a combination of three drugs leading to durable viral suppression) has expanded globally, resulting in a substantial decline in mortality rates and increased life-expectancy among children. Thus escalating numbers of children, who would previously have died in infancy and early childhood from untreated HIV infection are now surviving to adolescence.[2] HIV has therefore changed from a life-threatening illness to a chronic, treatable, albeit incurable, condition.

In adults with well-controlled HIV infection on ART in high-income countries, a range of comorbidities, including cardiovascular, renal, neurocognitive and lung disease, have been described and termed "non-AIDS-defining illnesses (NADIs)". This is in contrast to the opportunistic infections and malignancies that occur at advanced stages of HIV disease as a consequence of HIV-mediated immunosuppression. Likewise, there is now increasing recognition that children with HIV (CWHIV), including those taking ART are also at risk of developing chronic multisystem comorbidities and concomitant disability.[3,4] There have been reports from some settings of a trend from infectious events to non-infectious morbidities associated with inflammation, immunodeficiency and drug toxicity as CWHIV age.[5]

Many of these comorbidities will be driven by underlying inflammation associated with HIV-infection. The spectrum of morbidities in children may differ from those in adults, likely related to the timing of HIV infection and /or ART initiation and the absence of traditional adult risk factors such as ageing, smoking and alcohol use. Furthermore, there may be differences in the epidemiology of comorbidities in CWHIV in different settings. In high-income settings, combination ART became available in 1996, whereas in much of SSA paediatric ART was introduced after 2004. In addition, CWHIV in SSA start ART much later than those in high-income settings. In a global meta-analysis of children who entered HIV care before ten years of age, the age at ART initiation among children in Africa was 7.8 years compared to 0.9 years in the United States.[6]

In this review, we discuss the spectrum of chronic morbidities in children growing up with HIV focusing on studies in SSA, the likely pathogenesis underlying the development of comorbidities and the implications for HIV care and management and HIV programmes that have hitherto largely focused on ART delivery.

Search strategy and selection criteria

This is a descriptive review on comorbidities associated with HIV infection in children, informed by clinical experience and expert opinion. We searched PubMed for articles published from January 2014 to July 2019, with MeSH terms for HIV, Africa, children and adolescents, and with MeSH and related terms for specific topic areas (e.g. "cardiac disease", "lung disease"). We also looked for relevant publications among our personal files. We did not set any language limits. Articles resulting from these searches and relevant references cited in those articles were reviewed. The final reference list was generated on the basis of relevance to the broad scope of this review.

HIV-related chronic comorbidities

Chronic lung disease

While the incidence of acute pulmonary infections in CWHIV has declined due to cotrimoxazole prophylaxis and ART, several studies have reported a substantial burden of chronic respiratory symptoms and signs among children growing up with HIV taking ART including cough, breathlessness, reduced exercise tolerance and hypoxia,[7-9] and reduced lung function predominantly airflow obstruction with little reversibility with bronchodilators.[10-11] This has been reported in the context of late initiation of ART in childhood. High-resolution computed tomography studies (HRCT) show mosaic decreased attenuation as the predominant radiological finding with or without bronchiectasis (Figure 1A).[12,13] Mosaic attenuation correlates strongly with reduced Forced Expiratory Volume in one second (FEV1), and together with hypoxia and irreversible airflow obstruction, these findings are consistent with constrictive obliterative bronchiolitis (OB).[12] Notably, radiological findings consistent with lymphoid interstitial pneumonitis, the most common cause of chronic lung disease among CWHIV in the pre-ART era, have become rare in the ART era.[12,14] OB is characterised by inflammation of the bronchiolar epithelium, leading to dense fibrous scarring with small airway obstruction, complicated by recurrent infections and bronchiectasis. It has been described following severe lower respiratory tract infections in young children, often with adenovirus

and more commonly in the Southern hemisphere.[15] In a study from South Africa, radiological features of OB were associated with a history of tuberculosis or severe pneumonia.[13] Plain chest radiography is insensitive for small airways disease: definitive diagnosis usually requires HRCT,[12] which is rarely available in low-income settings. Bronchiectasis is also a well-recognised and irreversible cause of chronic lung disease among CWHIV, and can occur as a sequela of lymphoid interstitial pneumonitis, of recurrent pulmonary infections including tuberculosis and possibly of HIV infection itself.[16]

Reports of paediatric HIV-associated chronic lung disease come mainly from low-income settings. This may be due to a higher prevalence of risk factors, including recurrent pulmonary infections in early life, delayed ART initiation, household air pollution, malnutrition and stunting.[17] Malnutrition during the first year of life may be associated with decreased lung function at one year of age and stunting is a marker of delayed somatic growth; therefore, it is possible that stunted children may have smaller lungs and reduced lung volume.[18]

Importantly, lung impairments and decreased lung function in childhood track through adult life and therefore pulmonary insults in childhood not only prevent an individual from reaching full potential lung potential but also increase risk of chronic lung disease in adult life (Figure 2A).[19-20] A South African study showed that lung function tracked over two years in adolescents with HIV who were well established on ART, and early life pulmonary tuberculosis or hospitalisation for lower respiratory tract infections was associated with reduced lung function.[10]

Availability of diagnostic modalities for chronic lung disease such as spirometry and HRCT in low-income settings is limited and therefore chronic respiratory symptoms are frequently empirically treated with repeated antibiotics and anti-tuberculosis therapy in high HIV prevalence settings where tuberculosis is common. The pathogenesis of HIV-associated chronic lung disease is poorly understood, and without specific management guidelines. However, prevention of pulmonary infections by ensuring routine vaccinations including pneumococcal conjugate vaccine,[21] annual influenza vaccination, early ART initiation, continued co-trimoxazole prophylaxis and use on isoniazid prophylactic therapy, avoidance of exposure to tobacco smoke and indoor air pollution and optimising nutrition may mitigate the burden of chronic lung disease among CWHIV and optimise lung health.

Cardiovascular disease

Recent studies from low-income countries have reported a high burden of HIV-associated cardiac abnormalities in CWHIV taking ART, with wide prevalence estimates between 14% to 89%, likely reflecting differences in selection of participants and measurements.[22-24] The spectrum of abnormalities include left ventricular (LV) systolic and diastolic dysfunction, LV hypertrophy, left atrial dilatation, isolated right ventricular (RV) dilatation, conduction abnormalities and in some cases pericardial thickening or effusion (Figure 1B and C).[23-25] In a South African cohort of adolescents with HIV, RV dysfunction was the most common form of cardiopulmonary dysfunction; cardiopulmonary dysfunction was associated with lower body mass index (BMI), height and past pulmonary tuberculosis.[26] Notably, in most studies, children were pauci-symptomatic. A prospective study in Zimbabwean CWHIV on ART reported the incidence of left and right echocardiographic abnormalities as 3.52 and 5.64 per 100 person-years, respectively.[27] This study also found that most abnormalities persisted at 18 months but either asymptomatic or without worsening symptoms.[27]

Much less attention has been given to assessment of vascular disease in CWHIV, although there is evidence from high-income countries that HIV and ART, particularly protease-inhibitor-based regimens, are associated with subclinical atherosclerosis even in younger individuals.[28] A recent South African study reported an increased risk of endothelial dysfunction in adolescents with PHIV compared to their age-matched HIV-negative peers.[29] Traditional risk factors for cardiovascular disease including age, hypertension, smoking, lipid abnormalities do not play a significant role in this age-group and HIV and/or ART may thus play a much more significant role in the pathogenesis of vascular disease.

The natural history and clinical significance of cardiac and vascular abnormalities is not clear. In contrast to findings from SSA, a study from the United States reported a decline in rates of cardiomyopathy in the era of ART.[30] The underlying mechanistic pathways are not understood and the cardiac and vascular abnormalities reported may reflect impairment acquired prior to ART initiation. Surveillance and studies to investigate pathogenesis and progression are needed to understand whether these abnormalities are likely to result in an increased risk of premature cardiac disease as CWHIV enter adulthood.

Renal and metabolic disease

Microalbuminuria is an early marker of glomerular injury and predicts further proteinuria development. Two studies from Tanzania and South Africa reported a variable prevalence of 20.4% and 8.5% respectively for microalbuminuria in CWHIV.[31,32] The children in the Tanzanian study were younger and more immunosuppressed, and microalbuminuria was strongly associated with immunosuppression, as well as haematuria.[31] Notably, carriage of G1 and G2 apolipoprotein-L1 (*APOL1*) gene variants is common in Africans and is associated with an increased odds of early renal disease, with HIV infection significantly augmenting risk.[33]

Tenofovir disproxil fumarate (TDF) is associated with an adverse effect on renal function. TDF is associated with wasting of low molecular weight proteins, phosphate and glucose and although slowly progressive, chronic kidney disease in uncommon.[34] Hyperphosphaturia secondary to tubular dysfunction can disturb renal-bone metabolic regulation, leading to progressive bone loss and hypophosphataemic osteomalacia, as observed in Fanconi syndrome.[34]

Older ART drugs such as stavudine, didanosine and early generation protease inhibitors were associated with abnormal fat distribution (lipo-dystrophy or –atrophy). While newer ART regimens currently in use are less toxic, there is little improvement in those with established abnormalities following switching to newer, less toxic ART.[35] ART is also associated with dyslipidaemia and insulin resistance; however, data are sparse for CWHIV in SSA. A study from South Africa of paediatric HIV clinic attendees currently taking either a lopinavir/ritonavir or efavirenz based ART regimen (and with 90% having taken stavudine previously) reported a 10% prevalence of insulin resistance using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index, and similar prevalence of dyslipidaemias.[36] Overall, 40% had either insulin resistance or at least one lipid abnormality. The adjusted mean LDL cholesterol increased by 0.24mmol/l for each year of cumulative lopinavir/ritonavir exposure. Notably, the median BMI of participants was only 15kg/m^2. In a trial comparing three different nucleoside reverse transcriptase inhibitor based regimens in children starting ART in Uganda, HOMA-IR increased significantly in all three arms 48 weeks after ART initiation, and correlated with monocyte activation.[37] Similarly, in another study, abacavir was associated with increased HOMA-IR in adolescents.[38] While the long-term effects of these abnormalities reported in cross-sectional studies are not known, insulin

resistance, dyslipidaemias and abnormal fat distribution are recognised risk factors for cardiovascular disease, hence monitoring is required. Switching to newer protease inhibitors such as atazanavir or darunavir in children taking lopinavir may improve lipid profiles.[39]

Musculoskeletal disease

HIV infection is associated with growth failure, manifesting as stunting (impaired linear growth) and pubertal delay with pubertal onset delayed by up to a year.[40-41] Stunting is more profound among CWHIV in low-income than those in high-income settings, likely reflecting higher background rates of undernutrition and intercurrent infections.[42]

Impaired growth may have a deleterious effect on musculoskeletal development and health across the life-course. Puberty is a critical period for musculoskeletal development and bone mass accrual. After cessation of linear growth and skeletal maturation, bone mass reaches a peak (peak bone mass [PBM]),[43] after which bone mass declines at varying rates through adulthood (Figure 2B). PBM accounts for 60% of lifetime osteoporosis risk,[44] with a 10% decrease in PBM doubling adult fracture risk.[45] Pubertal delay predicts lower adult bone mass and increases future osteoporotic fracture risk.[46] A systematic review of 32 studies found an increased prevalence of low bone density in CWHIV, and HIV appears to be associated with decreased bone accrual throughout childhood and adolescence.[47] The majority of the studies were however from high-income settings and varied with respect to comparison groups, methods of measurement and adjustment for body size or growth retardation. A recent study from Zimbabwe showed reduced size-adjusted (Z-Score $\leq$ -2.0) lumbar spine total-body-less head bone density measurements in 15% and 13% of CWHIV aged 8 to 16 years taking ART.[48] Notably, this study used 'gold-standard' size adjustment methods for analysing dual X-ray absorptiometry scans which, if ignored, underestimate bone density in stunted children.[49]

Certain ART drugs such as TDF may cause accelerated bone loss, likely aggravated by both low body mass and vitamin D deficiency.[34] While studies have reported an association of TDF with lower bone density in CWHIV, this association may not be sustained longterm and longitudinal studies from SSA are needed to determine the impact of TDF on bone health in children.[34,48,50] Additional factors, prevalent among CWHIV, can further compromise bone health, including low muscle mass, poor nutrition, inadequate dietary calcium, vitamin D deficiency and the HIV-associated pro-inflammatory milieu.[51-53] Muscle strength and bone strength are closely related; muscles exert forces on bone resulting in bone adaptation in size

and strength.[54] HIV infection and consequent ill-health may reduce physical activity levels, impairing muscle strength (Figure 2C) and skeletal impact loading, and thus bone development.[55]

Although catch-up growth occurs after ART initiation, children who have more profound stunting and begin ART in later childhood have a delayed "growth spurt" and are typically unable to achieve their height potential.[42,56,57] Age at ART initiation is an important predictor of bone density. In the Zimbabwe study, CWHIV starting ART after the age of eight years had, on average, at least a one standard deviation lower size-adjusted lumbar spine bone density.[48] This level of bone density reduction doubles fracture risk in adults.[58] Given the late average age at ART initiation of CWHIV in SSA, these findings are concerning.[6]

Developmental delay, neurocognitive disease and mental health

In the pre-ART era, severe neurodevelopmental delay and HIV encephalopathy were common in CWHIV; the prevalence of HIV-associated neurocognitive impairment has declined in the ART era. Early ART initiation and viral suppression in infancy improves neurocognitive outcomes.[59] However, CWHIV who start ART outside early infancy can experience subtle to severe neurocognitive deficits. In a prospective study of children aged 5-11 years from four SSA countries that compared neuropsychological outcomes in those with HIV with those who were HIV-exposed, uninfected and those who were HIV-unexposed, CWHIV performed worse in all cognitive domains than the other two groups. More than 95% of CWHIV had a suppressed HIV viral load and good immunological status (CD4% ≥25%), but only 1% started ART in the first six months of life.[60]

An MRI study found that white matter (WM) structural abnormalities occur very early after birth, and even ART initiation by eight weeks of age may be too late to prevent HIV-associated WM abnormalities in the central nervous system.[61] Second line ART, a high HIV viral load, low CD4 counts and poor cognitive function were associated with poor WM integrity measured by diffuse tensor imaging in CWHIV in a South African study.[62] A recent meta-analysis demonstrated an association between HIV infection in children and adolescents and neurocognitive impairment, mainly in the domains of working memory, executive function and processing.[63] There was also some evidence of deficits in visual memory and visual-spatial ability. Geographic bias was notable with only a third of studies coming from SSA. The causes of neurocognitive impairment despite effective ART are likely multifactorial, including

ongoing viral replication in the central nervous system (CNS) and neuroinflammation, irreversible CNS injury prior to ART, neurotoxic effects of ART; and may be compounded by socioeconomic and psychosocial factors.[64] Children with neurocognitive impairment may appear asymptomatic with deficits missed by routine testing. There is a lack of context-specific and culturally validated screening tools or standardised definitions. One study in South Africa has recently validated a youth International HIV Dementia Screen.[65]

Several studies report a high prevalence of mental health disorders among children and adolescents with HIV. A large Ugandan study that recruited more than 1300 children and adolescents with HIV reported a prevalence of 17% of any psychiatric disorder and a 10% prevalence of a behavioural disorder most commonly attention deficit hyperactivity disorder. These disorders were more common in adolescents than in children and commonly occurred concurrently.[66] Similarly a study from South Africa reported that adolescents with HIV had poorer functional competence, self-concept and motivation and higher levels of depression, disruptive behaviour, attention-deficit hyperactivity disorder symptoms and clinically significant anger, compared to their HIV-negative peers.[67] CWHIV face recurrent and cumulative psychosocial stressors that differ from other chronic childhood illnesses such as stigma and discrimination, responsibility for welfare of siblings or other ill family members, illness and the death of their parents and unstable guardianship. This may hamper development of protective mechanisms and leave children psychologically vulnerable and ill-equipped for coping with challenges, likely increasing the risk of development of mental disorders.[67-69] It is possible that the neuropathological effects of HIV infection may augment risk.[70] Mental health disorders impact adherence to ART and are associated with an impaired quality of life, yet they typically receive little attention in the face of physical health concerns.

Malignancy

As CWHIV reach adolescence and become sexually active, they are at risk of acquiring Human Papilloma Virus (HPV) infection, with certain subtypes (e.g. 16 and 18) known to cause cervical cancer. The risk may be higher in those with HIV; in an Asian study, perinatally-infected adolescent females had a higher prevalence of high-risk HPV and abnormal cervical cytology than uninfected adolescents, after adjusting for age, sexual history and pregnancy. [71] The quadrivalent HPV vaccine was safe and highly immunogenic in boys and girls with HIV in a study from Kenya.[72] WHO recommends a 3-dose series (0,1-2, 6 months) for females with HIV rather than the standard two dose series (given to immunocompetent females <15 years

old), following studies that showed lower antibody titres post HPV vaccination in HIV-infected compared to uninfected women.[72,73] HIV testing prior to vaccination is not recommended which may mean that adolescents with HIV may miss the 3rd dose if vaccination programmes are implemented in schools.

CWHIV with advanced immunosuppression prior to ART or who started ART at an older age have an increased risk of cancer compared to those with modest immunosuppression or who began ART in infancy.[74] Reliable cancer incidence estimates in CWHIV are difficult to generate as many cancer registries do not report HIV status, and cancer incidence rates vary according to regions and study periods. Linked data from five paediatric ART programmes and four paediatric oncology units in South Africa showed an overall incidence rate of cancer of 82/100,000 person-years. The most common cancers were Kaposi's Sarcoma (KS) and non-Hodgkin's lymphoma (NHL), with incidence rates of 34 and 31/100 000 person- years respectively.[75] The risk of developing cancer was reduced by 70% for those children on ART, and risk increased with age at enrolment and immunodeficiency at enrolment. The risk of KS is limited to CWHIV in or from SSA. A study reported KS incidence rates of 81, 86, 11 per 100 000 person-years in children from SSA living in Europe, Eastern Africa and Southern Africa respectively, with no KS cases in children of non-SSA origin in Europe and in Asia.[76] Data from Malawi suggest that KS rates are increasing. The average annual number of new KS diagnoses was 18 cases per year from 2006-2010, increasing to 25 cases per year from 2011 to 2015, despite improved access to ART.[77] Although this could be explained by increased awareness and detection, it is also possible that the cumulative risk of malignancy increases with age even in the era of ART. An older study from the United States that followed children for ten years showed that whilst the incidence of KS and NHL decreased in the ART era, the risk of developing non-AIDS-defining cancers did not.[78] This highlights the need for continued monitoring of children growing up with HIV. Access to comprehensive cancer services remains limited in most low-income settings and mortality remains high.

Other comorbidities

In addition, there are other comorbidities that are common among CWHIV such as visual and hearing impairment and dental disease even in the ART era.[79-82] Skin disease is severe and atypical, responds less well to treatment, and relapse more frequently compared with HIV-uninfected children. Although incidence has declined in the ART era, HIV-related skin conditions remain one of the most common management problems faced by health care

workers caring for CWHIV. ART is associated with risk of drug reactions and immune reconstitution inflammatory syndrome skin disease (unmasking of new skin disease or paradoxical worsening of existing dermatological conditions).[83] These conditions receive little attention as they may not be "life-threatening" but lead to complications and disability, reduced quality of life and frequent clinic attendances placing an additional burden on health services.

Pathogenesis of chronic co-morbidities

The mechanisms underlying the comorbidities described in association with PHIV infection are largely unknown. Some of the underlying mechanisms may be shared with those seen in adult HIV infection, whilst others may be unique to the paediatric age-group, in keeping with the distinct clinical features observed in this age-group. Pathogenic mechanisms may also differ between populations in high and low-income settings.

In adults, the development of HIV-associated comorbidities is thought to be related to levels of persistent immune activation, predominantly reflecting activation of monocytes and macrophages, rather than T-cell activation.[84] A number of biomarkers have been described, largely in cross-sectional studies, that associate with adult comorbidities.[85] These include inflammatory markers such as Interleukin 6, soluble tumour necrosis factor receptors I and II (sTNFR-I and sTNFR-2), Interferon-inducible Protein 10 (IP10) and high sensitivity C-reactive protein, markers of monocyte activation such as soluble CD14 and CD163, markers of indoleamine 2,3-dioxygenase-1 activity, markers of coagulation risk, particularly D-dimer levels, and markers of gut barrier dysfunction, Zonulin and intestinal fatty acid binding protein. In longitudinal studies, rising levels of these biomarkers better predicted the development of NADIs than a single value at recruitment.[86] These findings suggest that impaired gut barrier function leads to the translocation of microbial products from the gut into the circulation, where they activate monocytes and macrophages, initiating a cycle of chronic inflammation.[85] This appears to be related to the activation of a specific subset of inflammatory monocytes which express Tissue Factor: these can secrete high levels of pro-inflammatory cytokines as well as trigger the coagulation cascade, so are particularly implicated in HIV-associated coagulopathy.[87]

Additional contributing factors to inflammation include vitamin D deficiency and cytomegalovirus (CMV) co-infection.[88] Vitamin D deficiency is associated with immune

activation levels in individuals with HIV, potentially mediated through its immunomodulatory effects on populations of monocytes and macrophages, dendritic cells, and B and T lymphocytes.[89] A trial of vitamin D supplementation in deficient CWHIV well-controlled on ART, led to significant reductions in both T-cell and monocyte activation.[90]

The relationship between comorbidities and CMV infection is difficult to disentangle, as virtually all individuals with HIV have CMV co-infection: however, in the few studies that include CMV-negative HIV-infected subjects for comparison, HIV/CMV co-infected people have higher plasma levels of IP-10, TNF-R2 and D-dimer,[91] and have an increased risk of NADIs, particularly cardiovascular and cerebrovascular disease.[92] In cohort studies, associations have been described between inflammatory markers, the development of comorbidities and levels of CMV IgG,[93,94] and CMV-specific T-cells,[95] implying that subclinical CMV reactivation/replication is reflected in elevated immune responses: however, it is important to control for ageing in these studies.[96] For CWHIV in low-income settings, especially when HIV diagnosis and ART initiation is delayed, it is likely that primary CMV infection occurs in infancy at a time of uncontrolled HIV replication. African children acquire CMV infection early in life, primarily through breastmilk exposure: in studies in The Gambia, 85% of infants had acquired CMV by 12 months of age, reaching 100% by 18 months.[97] Thus, their situation is distinct from that of adults who mainly acquire HIV after CMV infection and would already have generated immune responses leading to long-term viral control. Therefore, CMV reactivation or reinfection may occur more frequently in late-diagnosed children with PHIV and could make a greater contribution to the pathogenesis of comorbidities. A recent study in Zimbabwe reported unexpectedly high levels of CMV viraemia in older CWHIV.[98] The detection of CMV DNA in plasma was associated with two of the major comorbidities described in older children with PHIV, chronic lung disease and stunting. Further studies are needed to determine whether similar findings are seen in other settings and if CMV DNA-aemia represents reactivation of latent infection or reinfection with new viral strains.

The other key difference between children and adults is the greater potential for lymphopoiesis with enhanced thymic and bone marrow activity: paediatric slow progressors are characterised by what was described as “supranormal” thymic activity.[99] However, thymic infection leading to impaired function can occur in a proportion of CWHIV, which is associated with significantly more rapid disease progression.[100] Several studies suggest that children with PHIV have markers of premature ageing,[101] including shorter telomere length,[102] distinct

epigenetic features of ageing,[103] and accumulation of senescent (CD28- CD57+) and exhausted (PD-1+) T-cells.[102] In these subjects there are also features of thymic dysfunction,[102] which could potentially indicate HIV infection of the thymus, leading to an inadequate response to T-cell turnover driven by immune activation.

In summary, comorbidities in CWHIV are likely to reflect persistent immune activation and premature aging of the immune system, potentially driven in low income settings by early-life infection with CMV and exacerbated by vitamin D deficiency (Figure 3). Interventions aimed at reducing inflammation, CMV suppression and/or vitamin D supplementation may have potential for control or even reversal of comorbidities and merit further study.

Recommendations for Policy and Research

While the access to paediatric ART has increased dramatically in the past decade, coverage in children lags behind that in adults with about 54% of CWHIV globally accessing treatment in 2018 compared to 62% of adults.[104] Timely diagnosis and treatment of HIV infection in children remains a critical priority.

In SSA, there is a large cohort of CWHIV entering adolescence and adulthood that has had delayed ART initiation, and are at increased risk of multi-system impairments and earlier onset of comorbidities that are usually associated with ageing. HIV care has to date mainly focused on delivery of and sustaining adherence to ART and there is an underappreciation of the burden of multisystem HIV-associated comorbidities among children. In addition, complex clinical issues place heavy demands on already overstretched health-care systems, and optimum screening and management strategies are not well defined. In response to this, the WHO convened two scoping meetings in 2014 and in 2019 to review available data and policies on management of major HIV-associated comorbidities as well as evidence gaps in clinical management and programming.

Comprehensive HIV care should include diagnosis and management of comorbidities and consequent disability. The Panel outlines suggestions for interventions and research priorities aimed at addressing HIV-associated comorbidities in children. In Africa, dedicated paediatric and adolescent HIV care services are the exception rather than the rule. Provision of comprehensive HIV care will need to extend beyond centres of excellence to low-level health-

care settings, integrate within existing HIV and maternal, newborn and child health platforms and consider the physiological and psychosocial changes through childhood. Importantly, inclusion of guardians, teachers and communities as equal partners will be critical to optimally support CWHIV achieve their full potential.

Contributors

RAF and LJF conceptualised and coordinated the review. RAF wrote the chronic lung disease section with SR-J, and collated the manuscript. RAF and EDM provided clinical pictures. SR-J wrote the pathogenesis section. LJF wrote the malignancy section. CLG and RR wrote the musculoskeletal section. EDM and HJZ wrote the cardiac disease section. JH wrote the neurocognitive and mental health section with input from LJF and RAF. JJ and CLG wrote the renal and metabolic disease section. WA and LM wrote the policy section with input from RAF and LJF. All authors contributed to editing and approved the final version of the manuscript.

Conflicts of interest

We declare that we have no conflicts of interests

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Disclaimer

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Panel: Addressing HIV-associated comorbidities in children and adolescents

Research priorities

Epidemiology and clinical spectrum

Pathogenesis

Diagnosis and screening

- Standard definitions of comorbidities based on population-specific normative ranges
- When to start and frequency of screening
- Age- and culturally appropriate screening tools for mental health and neurocognitive disease

Interventions for prevention and treatment

- Preventive and therapeutic drugs: e.g. antibiotics, antivirals, anti-inflammatory drugs, Vitamin D
- Feasible and effective educational and mental health interventions
- Interactions of drugs used for prevention/treatment with antiretroviral therapy

Service delivery

- How to integrate diagnosis and management of HIV-associated comorbidities within HIV services and/or maternal, newborn and child health platforms

Components of comprehensive HIV care

- Earlier initiation of antiretroviral treatment to prevent complications
- Monitoring growth, musculoskeletal and neurocognitive development
- Screening for cardiac, lung and renal disease
- Assessment of psychosocial status (schooling, guardianship) and mental health
- Management of common mental health disorders and psychosocial support
- Isoniazid and cotrimoxazole prophylaxis
- Optimal nutrition
- Catch up or re-vaccination according to WHO guidelines e.g. pneumococcal and influenza vaccination
- Human papillomavirus vaccination for adolescents
- Cervical cancer screening after sexual debut
- Referral to clinical specialties for management
- Liaison with disability and rehabilitation services
- School-based programmes to provide educational support
- Leverage existing early child development platforms for supporting CWHIV
- Linkage to community-based psychosocial support services

Key Points

Despite antiretroviral therapy, longstanding HIV infection in children is associated with multisystem chronic comorbidities, particularly in sub-Saharan Africa where HIV treatment initiation is often delayed and occurs much later in childhood than in high-income settings

Chronic morbidities in children with HIV are driven by underlying dysregulated immune activation associated with HIV infection, or are a sequelae of infections and/or HIV treatment

HIV programmes have predominantly focused on delivery of antiretroviral therapy and there has been much less attention paid to diagnosis and management of chronic comorbidities

Validated tools for screening and diagnosis and evidence-based interventions for prevention and treatment of comorbidities need to be developed

As well as earlier initiation of antiretroviral therapy, HIV care programmes need to identify an address the additional health needs of children with chronic complications including educational support, rehabilitation, nutrition, psychosocial and mental health support, if children with HIV are to achieve optimal health outcomes.

Figure Legends

Figure 1: Clinical comorbidities associated with HIV infection in children and adolescents

A) High resolution computed tomography scan showing bilateral "black and white" lung (mosaic attenuation pattern) with decrease in the number and calibre of vessels (arrow). There is also atelectasis on the right and bronchiectasis.

B) Parasternal long axis view (i)) and Apical 4-chamber view (ii) of a 12-year-old female with dilated right ventricle (RV), left ventricle (LV), right atrium (RA) and left atrium (LA) and pericardial effusion (PE).

Figure 2: Hypothesised effect of HIV infection on respiratory function (adapted from reference 20) (A), bone mass (adapted from reference 47) (B) and muscle strength (C) across the life-course

Figure 3: Pathogenesis of HIV-associated comorbidities